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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,357	09/20/2003	Craig A. Rosen	PS901	5455

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
10/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,357	ROSEN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,16,21,24-29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-12, 16 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed November 1, 2006 on February 1, 2007, is acknowledged. Exhibits filed with the instant application have been considered.

Claim Disposition

2. Claims 11-12, 16, 21, 24-29, and 31-32 are pending. Claims 11-12, 16 and 25-29 are under examination.

Withdrawn-Specification Objection

3. Previous objections to the specification are withdrawn by virtue of submission of an amendment.

Withdrawn-Sequence Compliance

4. Previous objections to the specification are withdrawn by virtue of submission of an amendment.

Withdrawn-Claim Rejections-Utility Rejections Under 35 USC § 101 And 35 USC 112, First Paragraph

5. Previous rejections to the claims under 35 USC 101 and 112, first paragraphs (in part) are withdrawn by virtue of submission of an amendment.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11-13, 16 and 25-29 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the protein set forth in SEQ ID NO: 4 08, does not reasonably provide enablement for any polypeptide fragment thereof or any polypeptide fragment thereof having the recited function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands,*

858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of fragments that are not supported by the instant specification. The claimed polypeptide once modified might not have the same properties of the native/wild-type protein or retain the same function. The claims recite language such as "at least 30 contiguous amino acids...wherein said fragment has promotes angiogenesis", however, no specific fragment is disclosed in the instant specification with the recited activity. The specification does not provide a protein having 30 residues promoting angiogenesis or any other fragment. Furthermore, a fragment comprising "at least 30 residues" is not limited and can produce all kinds of structures with that open language that applicant has no support for in the instant specification, nor shows any correlation between the recited function and the structures encompassed in this claim. With the modifications contemplated said protein could be a completely different protein from a different protein class with a different function or no function. Note also that the claims do not set forth where variations will occur or what variations can be tolerated in the sequence. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. In the instant application, the partial structure in the form of the recited percent identity is insufficient to determine a chemical structure for the variants encompassed in the claims.

Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. The specification provides general teaching with respect the

recited function, thus there is no showing of any fragments or even the full-length protein having said function. Furthermore, claim 11 parts (e-g) remain directed to a polypeptide encompasses a genus of structures and no function is associated with the protein *per se.* Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells,

Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain function. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

7. Claims 11-13, 16 and 25-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a polypeptide comprised in SEQ ID NO:408 (see claim 11). The claimed invention is encompass a genus of fragments of the protein in (SEQ ID NO:408), however, no function is associated with the protein *per se* (see claim 11 e-g). Absent functional language, the skilled artisan would not know if said fragments had the same function as the wild-type or a different function. The specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention. It is noted that the claims have been amended to recite that the claimed protein promotes angiogenesis, however, the specification provides no showing of any fragments with said function.

Thus, in view of the foregoing the claimed invention lacks proper written description and the skilled artisan cannot envision the detailed chemical structure of all the claimed fragments encompassed by the claims. Additionally, the instant specification has not provided a representative number of species for the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed

genus. The claimed genus of polypeptides could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed polypeptides encompasses widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Withdrawn-Claim Rejections- 35 USC 112, Second Paragraph

8. Previous rejections to the claims under 35 USC 101 and 112, first paragraphs (in part) are withdrawn by virtue of submission of an amendment.

Response to Applicant's Arguments:

9. Applicant's arguments have been fully considered. Note that the utility rejection and the portion of the 112 first paragraph pertaining to utility and deposit information is withdrawn. In addition, the 112 second paragraph rejection is withdrawn. The arguments pertaining to the utility rejection are moot because the rejection has been withdrawn based on the insertion of an asserted utility, however, note that the utility given to the claims are not enabled as stated above, applicant's arguments are not deemed persuasive for the following reasons. With regard to the remaining portion of the 112 first paragraph enablement and written description which have been amended in view of the withdrawal of the utility rejection and based on amendments to the claims, applicant's traversal is discussed herein.

Applicant's state on page 11 that the claims have been amended to recite "at least 30 or 100 contiguous amino acids that have a specific biological activity, promoting angiogenesis". This argument is not persuasive. Firstly portions of claim 11 for example recites this activity, however, items such as (e-g) recite no function and encompass fragments with the language "a polypeptide comprising amino acids 1-218 of SEQ ID NO:408". This portion of the claim for example reads on any fragment of SEQ ID NO:408 and is not limited to residues 1-218 with the open language comprising. Secondly, the instant specification generally discloses the recited

function and no real association is made between the encompassed fragments and said biological activity. For example the specification discloses that , "angiogenesis... indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), diseases and/or disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders"), diseases and/or disorders involving cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level"), diseases and/or disorders involving angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity"), to promote or inhibit cell or tissue regeneration (e.g., as described below under "Regeneration"), or to promote wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation")". However, the instant specification does not provide any showing of any fragments of SEQ ID NO:408 in association with promoting angiogenesis, furthermore the issue is that the claims read on an enormous amount of fragments that applicant is not in possession of hence the written description rejection and is not supported by the instant specification hence the enablement rejection. Moreover, there is no structure function correlation made and the assertion of the recited function does not endow said function to all the fragments encompassed in the claims. Absent showing of a fragment such as a fragment having 30 contiguous residues producing the effect of promoting angiogenesis, then that function is not garnered just by mere recitation.

Applicant further states that the enablement requirement is satisfied if the specification enables a person of ordinary skill in the art to practice a single use of the claimed polypeptide.

This argument is not persuasive in view of the prophetic teaching in the specification with regard to "promoting angiogenesis" as indicated above. Applicant's states that the Federal Circuit has held that making the claimed species and screening them for function is acceptable, as long as the experimentation is not undue. Applicant is correct in this statement, however, the claimed invention is directed to an invention that requires undue experimentation. The claimed invention is an invitation to one of ordinary skill in the art to engage in further experimentation, to first produce all the enormous fragments encompassed in the claims and then test the same for function. The claimed language for example in claim 11 (e) encompasses a dipeptide, thus is not directed to for example "the residues 1-218 of SEQ ID NO:408". In addition, the claims encompass "any heterologous amino acid" (see claim 12) comprised in the claimed polypeptide having any structure. Additionally the claims do not set forth that "the residues 1-218 of SEQ ID NO:218 of SEQ ID NO:408", for example, has the recited function. The experimentation involved is in no way routine and is undue. As the written description and enablement rejections are intertwined and the response to the issues raised is similar the two have been discussed together herein. As set forth above this make and test position is not consistent with *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

On page 12 applicant in discussing the written description rejection states that the instant specification discusses many biological functions associated with the claimed polypeptides in

Table 1D. Applicant is correct in that the specification provides several asserted utility, however there is no showing of any specific biological function in association with the claimed products. The disclosure in the instant specification is simply prophetic. Thus applicant's statements have been considered but are not persuasive. The claims are not directed to a specific fragment with a demonstrated function or a full-length polypeptide having the same function. Thus, the rejection remains.

Conclusion

10. No claims are allowable.

11. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS 9/20/07

Primary Examiner